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# Cyclization of 2-Alkynylallyl Alcohols to Highly Substituted Furans by Gold(I)–Carbene Complexes

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**Keywords:** Carbene ligands / Cycloisomerization / Allylic compounds / Gold / Oxygen heterocycles

Various 2-alkynylallyl alcohols were synthesized by a generally applicable Sonogashira coupling protocol. Subsequent gold-catalyzed transformation was investigated. The use of $Au^I$ catalysts bearing carbene ligands, of either the N-heterocyclic carbene or nitrogen acyclic carbene type, delivered the desired products with low catalyst loadings and under very mild reaction conditions. A broad array of substrates was tested, including alkyl-, alkenyl-, and aryl-substituted alkynes, as well as substrates with two alkynyl moieties. The methodology turned out to have a broad scope. Secondary allyl alcohols were also tolerated, and the resulting trisubstituted furans could be isolated in high yields.

## Introduction

Furans are among the most important five-membered heterocycles in organic and pharmaceutical chemistry.[1] They are not only significant as key motifs in many natural products, but also as versatile building blocks for the construction of highly complex target structures in numerous total syntheses.[2] As an alternative to classical furan syntheses, the use of transition metals as catalysts for atom-economic transformations of noncyclic substrates to furans has become a fast growing field of research in the last years.[3] In contrast to the often harsh conditions of the classical methods, most of these reactions can be performed under very mild reaction conditions and within short reaction times.[4] In this context, the cyclization of 2-alkynylallyl alcohols to highly substituted furans offers a very attractive synthetic tool. Besides easy access to the starting materials, the installation of substituents in the 3-position of the furan ring usually causes great synthetic difficulties but might be addressed easily by this route. When we started our investigation, gold as highly alkynophilic catalyst had not been tested for this transformation. Besides base-catalyzed cyclizations (potassium *tert*-butoxide or KOH/Aliquot 336 at 25–60 °C),[5] there were reports on the use of palladium (5 mol-% $PdOAc_2$, 100 °C, 24 h),[6] molybdenum [15 mol-% $Mo(CO)_6$, irradiation, 15 h],[7] and silver catalysts (10 mol-% $AgNO_3$ on $SiO_2$ at room temp.,[8a,8b] 5 mol-% AgOTf,[8c] 80 °C). During our investigation, a $AuBr_3$-catalyzed version was published for the construction of fused furans.[9] Here we report on our general protocol for the gold-catalyzed[10] version of this reaction, having the advantage of both low catalyst loadings as well as mild reaction conditions.

## Results and Discussion

The 2-alkynylallyl alcohols were prepared by Sonogashira coupling of 2-haloallyl alcohols **2** with terminal alkynes with catalyst loadings of 2.5 mol-% of $(PPh_3)_2PdCl_2$/CuI. Substituted 2-iodoallyl alcohols **2** were easily accessible according to known literature procedures.[11] The results for the Sonogashira couplings are summarized in Table 1.

The yields of the Sonogashira coupling were good to excellent in most cases. The scope of this coupling reaction was high, which is demonstrated by the tolerance of different aromatic alkynes (Table 1, Entries 1–6) as well as alkyl-substituted alkynes (Table 1, Entries 7–9). In the case of an additional double bond directly attached to the alkyne (Table 1, Entry 10) a significantly lower yield was observed. Bifunctional alkynes could also be converted in excellent to moderate yields (Table 1, Entries 11 and 12). Variation of the allyl alcohols led to a slight drop in yield for secondary alcohols (Table 1, Entries 13 and 14). In the case of trisubstituted alkenes, no isomerization of the double bond was observed (Table 1, Entries 15 and 16) and yields were also reasonable.

Initial screening towards the optimal reaction conditions for the gold-catalyzed transformations was performed with test substrate **3a** in dichloromethane (Table 2). With a loading as small as 0.3 mol-% of catalyst, 100% GC yields were detected for gold(I) complexes with carbene ligands, no matter if an NAC[12] (nitrogen acyclic carbene; Table 2,

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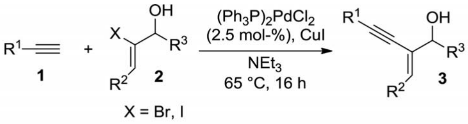
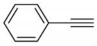
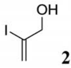
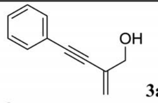
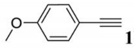
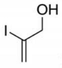
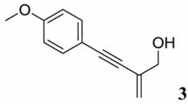
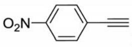
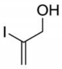
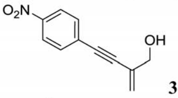
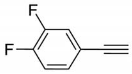
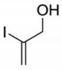
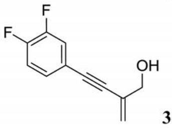
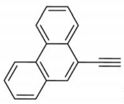
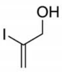
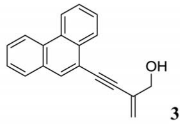
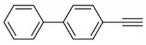
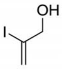
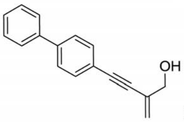
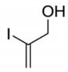
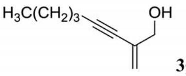
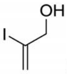
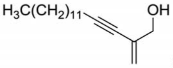
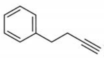
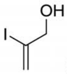
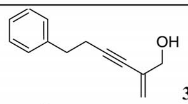
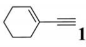
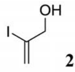
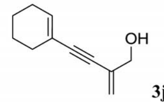
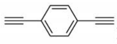
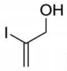
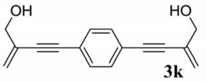
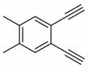
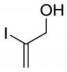
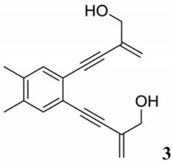
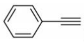
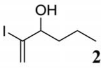
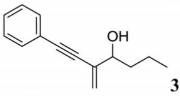
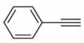
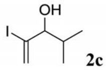
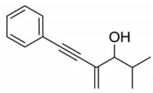
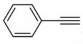
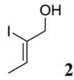
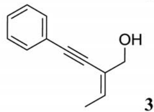
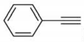
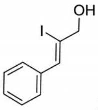
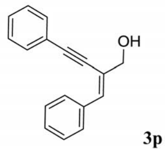
Table 1. Sonogashira coupling of 2-haloallyl alcohols **2**.

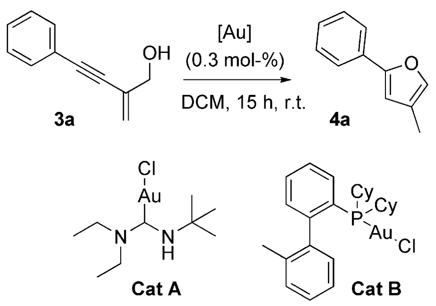


| Entry | Alkyne **1** | Allyl alcohol **2** | Product **3** | Yield [%] |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | >99 |
| 2 |  **1b** |  **2a** |  **3b** | 43 |
| 3 |  **1c** |  **2a** |  **3c** | 59 |
| 4 |  **1d** |  **2a** |  **3d** | 82 |
| 5 |  **1e** |  **2a** |  **3e** | 95 |
| 6 |  **1f** |  **2a** |  **3f** | 88 |
| 7 | $H_3C(CH_2)_3{-}{\equiv}$ **1g** |  **2a** |  **3g** | 78 |
| 8 | $H_3C(CH_2)_{11}{-}{\equiv}$ **1h** |  **2a** |  **3h** | 42 |
| 9 |  **1i** |  **2a** |  **3i** | 62 |
| 10 |  **1j** |  **2a** |  **3j** | 68 |
| 11 |  **1k** |  **2a** |  **3k** | >99 |
| 12 |  **1l** |  **2a** |  **3l** | 39 |
| 13 |  **1m** |  **2b** |  **3m** | 78 |
| 14 |  **1n** |  **2c** |  **3n** | 38 |
| 15 |  **1o** |  **2d** |  **3o** | 66 |
| 16 |  **1p** |  **2e** |  **3p** | 73 |

Entry 1) or an NHC (N-heterocyclic carbene) ligand (Table 2, Entry 2) was used. Phosphane ligands for the $Au^I$ catalysts only delivered poor results under the same reaction conditions (Table 2, Entries 3 and 4). The neutral gold(I) chloride or the coordinatively saturated (IPr)AuCl, without activation by a silver salt, gave no conversion (Table 2, Entries 5 and 6). Gold(III) sources were also effective (Table 2, Entries 7 and 8), but yields turned out to be lower than those obtained with the above-mentioned systems.[13] The coordinatively saturated gold(III) species were all inactive (Table 2, Entries 9–11). Control experiments with *p*TsOH as well as other transition metals like silver and copper showed no reactivity (Table 2, Entries 12–14). Compound **4a** could be obtained as crystals, which were suitable for X-ray crystal structure analysis.[14] Figure 1 shows the solid-state molecular structure of the resulting 1,3-disubstituted furan.

Due to the superior yields for the gold(I) catalysts as well as their reduced Lewis acidity, we examined the substrate scope under the optimized conditions from Table 2 (either Entry 1 or 2). In order to keep the reaction time short, all substrates were converted with 1.0 mol-% of gold catalysts under open flask conditions. All the reactions were stopped after 1 h, a time when complete conversion was reached for all tested substrates. The results are outlined in Table 3. For aromatic substrates, the reaction delivered excellent to moderate yields, depending on the electronic properties of the systems. For comparison of the two carbene-type ligands, substrate **3b** was converted with both types of ligands and yields turned out to be equal (Table 3, Entry 2). Electronically neutral and electron-rich systems (Table 3, Entries 1 and 2) were excellent, whereas the increased electronic deficiency of starting materials **3c**,**d** (Table 3, Entries 3 and 4) led to significantly lower yields. A slightly lower yield was

Table 2. Catalyst screening for model substrate **3a**.



| Entry | Catalyst[a] | Yield (GC) [%][b] |
|---|---|---|
| 1 | cat. A/$AgSbF_6$ | 100 |
| 2 | (IPr)AuCl/$AgSbF_6$ | 100 |
| 3 | **Cat. B**[15]/$AgSbF_6$ | 6 |
| 4 | $PPh_3AuCl/AgSbF_6$ | 2 |
| 5 | AuCl | 0 |
| 6 | (IPr)AuCl | 0 |
| 7 | $AuCl_3$ | 40 |
| 8 | $AuBr_3$ | 73 |
| 9 | $NaAuCl_4 \cdot 2H_2O$ | 0 |
| 10 | $NaAuBr_4$ | 0 |
| 11 | $HAuCl_4 \cdot xH_2O$ | 0 |
| 12 | *p*TsOH | no conversion |
| 13 | $AgSbF_6$ | no conversion |
| 14 | CuI | no conversion |

[a] Catalyst loading of 0.3 mol-%. [b] Internal standard tetradecane.

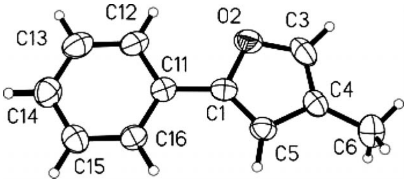
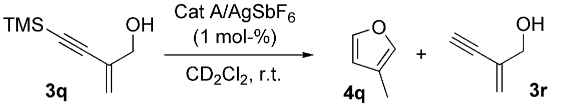


Figure 1. Solid-state molecular structure of compound **4a**.

also monitored with phenanthrene-substituted alkyne **3e**; here the increased steric demand could be the reason. Biphenyl substrate **3f** showed higher reactivity again, yielding 79% of furan **4f** (Table 3, Entry 6). Next we explored the reactivity of alkyl-substituted alkynes. While complete conversion after 1 h was also observed for these systems, only moderate to good yields were observed (Table 3, Entries 8–10). Surprisingly, even substrate **3j** bearing an enyne moiety could be converted; no polymerization of electron-rich styrene analogue **4j** was observed, once again revealing the exceptionally mild conditions of this methodology. Substrates **3k** and **3l**, which contain two reactive moieties, also underwent the expected conversion, but yields differ dramatically between the different substitution patterns (76% for substrate **3k** vs. 14% for **3l**). Similar to other substrates the steric influence in the β-position of the reacting alkyne carbon seems to play an important role. The use of secondary alcohols as starting materials was also possible. Here no steric limitations occurred, despite the fact that yields were even higher for the sterically more demanding isopropyl substituent in substrate **3n** (Table 3, Entry 14). No significant change was observed by variation of the $R^2$ substituents of substrates **3o** and **3p** (Table 3, Entries 15 and 16) and once again yields were good to excellent.

We also tested a silylated alkyne, substrate **3q**, with **Cat. A**; under the normal reaction conditions from Table 3, 3-methylfuran (**4q**) was produced in 47 and 50% yield accompanied by up to 21% of desilylated **3r** after 1.5 and 8 h, respectively. It seems that desilylation is an efficient process under these conditions, and at the same time the complete disappearance of **3r** after 3 d indicated that **3r** decomposed under the reaction conditions. This was confirmed with a sample of pure **3r** (obtained by normal desilylation of **3q** with $K_2CO_3$ in methanol), which slowly decomposed but even after 3 h did not show any trace of **4q** under the same conditions (Scheme 1).



| | Yield [%] 4q | Yield [%] 3r | Conversion [%] |
|---|---|---|---|
| 20 min | 18 | 2 | 28 |
| 1.5 h | 47 | 21 | 92 |
| 8 h | 50 | 21 | 100 |
| 3 d | 50 | 0 | |

Scheme 1. Involvement of a silylated but not a terminal alkyne.

## Conclusions

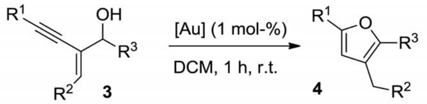
This gold(I)-catalyzed cyclization of easily accessible 2-alkynylallyl alcohols is of broad scope and allows the efficient synthesis of 2,4-disubstituted and 2,3,5-trisubstituted furans under mild conditions. The transformation of even bifunctional substrates to the corresponding bisfurans opens interesting aspects for synthetic chemistry. Possible applications of this method are currently under investigation and will be reported in due course.

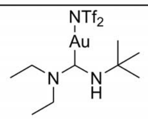
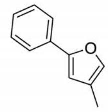
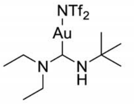
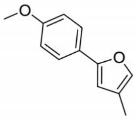
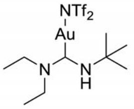
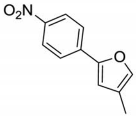
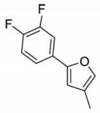
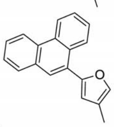
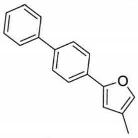
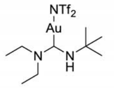
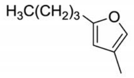
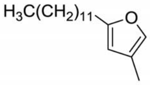
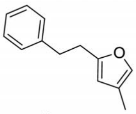
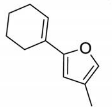
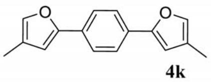
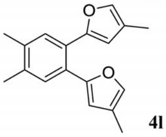
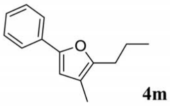
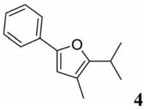
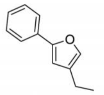
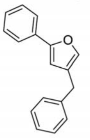
## Experimental Section

**General Procedure for the Preparation of Alkynylallyl Alcohols 3:** Alkynylallyl alcohols **3** were prepared under common Sonogashira conditions:[16] Acetylene **1** (1.2 equiv.) and vinyl iodide **2** (1 equiv.) were dissolved in degassed $NEt_3$ (20 mL) under nitrogen atmosphere. To this solution was added $Pd(PPh_3)_2Cl_2$ (2.5 mol-%). After 10 min, copper(I) iodide (2.5 mol-%) was added. The mixture was heated at 65 °C for 16 h. After cooling to room temperature, the solvent was removed in vacuo. The crude product was purified by column chromatography.

**General Procedure for the Gold(I)-Catalyzed Preparation of Furans 4:** Alkynylallyl alcohol **3** (1 equiv.) was dissolved in dichloromethane (5 mL). To this mixture was added a solution of the gold(I) catalyst (1 mol-%) and $AgSbF_6$ (1 mol-%). After stirring at room temperature for 1 h, the solvent was removed in vacuo, and the crude product was purified by column chromatography.

Table 3. Substrate scope of the gold(I)-catalyzed cyclization of 2-alkynyl-allylalcohols.



| Entry | Starting material | Catalyst[a] | Product 4 | Yield [%] |
|---|---|---|---|---|
| 1 | **3a** |  |  **4a** | 98 |
| 2 | **3b** |  |  **4b** | 91, 89[b] |
| 3 | **3c** |  |  **4c** | 76 |
| 4 | **3d** | IPrAuCl/ AgSbF$_6$ |  **4d** | 56 |
| 5 | **3e** | IPrAuCl/ AgSbF$_6$ |  **4e** | 56 |
| 6 | **3f** | IPrAuCl/ AgSbF$_6$ |  **4f** | 79 |
| 7 | **3g** |  |  **4g** | 54[c] |
| 8 | **3h** | IPrAuCl/ AgSbF$_6$ |  **4h** | 65 |
| 9 | **3i** | IPrAuCl/ AgSbF$_6$ |  **4i** | 56 |
| 10 | **3j** | IPrAuCl/ AgSbF$_6$ |  **4j** | 60 |
| 11 | **3k** | IPrAuCl/ AgSbF$_6$ |  **4k** | 76 |
| 12 | **3l** | IPrAuCl/ AgSbF$_6$ |  **4l** | 14 |
| 13 | **3m** | IPrAuCl/ AgSbF$_6$ |  **4m** | 56 |
| 14 | **3n** | IPrAuCl/ AgSbF$_6$ |  **4n** | 84 |
| 15 | **3o** | IPrAuCl/ AgSbF$_6$ |  **4o** | 71 |
| 16 | **3p** | IPrAuCl/ AgSbF$_6$ |  **4p** | >99 |

[a] Catalyst loading of 1.0 mol-%. [b] Using IPrAuCl/AgSbF$_6$ as catalyst system. [c] Volatile; unstable in solution.

**Supporting Information** (see footnote on the first page of this article): Procedures and spectroscopic data of all reported compounds.

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